July 14, 2005

Vicente Santa Cruz, Ph.D.
Product Stewardship, Toxicology
Chevron Phillips Chemical Company LP
10001 Six Pines Drive
Suite 4103
The Woodlands, TX 77380

Dear Dr. Santa Cruz:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for 2,5-Dihydrothiophene 1,1-dioxide (Sulfolene) posted on the ChemRTK HPV Challenge Program Web site on April 19, 2004. I commend Chevron Phillips Chemical Company for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that Chevron Phillips advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission. Please send any electronic revisions or comments to the following e-mail addresses: oppt.ncic@epa.gov and chem.rtk@epa.gov.

If you have any questions about this response, please contact Mark Townsend, Acting Chief of the HPV Chemicals Branch, at 202-564-8617. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

/s/

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: M. E. Weber
J. Willis

EPA Comments on Chemical RTK HPV Challenge Submission:
2,5-Dihydrothiophene 1,1-dioxide (Sulfolene)

Summary of EPA Comments

The sponsor, Chevron Phillips Chemical Company LP, submitted a test plan for 2,5-dihydrothiophene 1,1-dioxide (sulfolene, CAS No. 77-79-2), a IUCLID Data Set for sulfolene, and robust summaries for the proposed analog, tetrahydrothiophene 1,1-dioxide (sulfolane, CAS No. 126-33-0), dated April 6, 2004. EPA posted the submission on the ChemRTK HPV Challenge Web site on April 19, 2004.

EPA has reviewed this submission and has reached the following conclusions:

1. Analog Justification. For health effects, the submitter proposed to use data for sulfolane to fill data gaps for the sponsored substance, sulfolene. This approach is not adequately justified in the test plan.

2. Physicochemical Properties. The data are adequate for the purposes of the HPV Challenge Program, except for boiling point and vapor pressure. The submitter needs to provide measured data for these endpoints on sulfolene.

3. Environmental Fate. The data are adequate for the purposes of the HPV Challenge Program. The submitter needs to incorporate the hydrolysis information from the test plan into the stability in water section of the sulfolene robust summary.

4. Health Effects. The data for the acute and genetic toxicity endpoints are adequate for the purposes of the HPV Challenge Program. EPA reserves judgement on the repeated-dose and reproductive/ developmental toxicity endpoints pending the submission of additional information. The submitter needs to address deficiencies in the robust summaries.

5. Ecological Effects. The data are adequate for the purposes of the HPV Challenge Program. The submitter needs to address deficiencies in the robust summaries.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA Comments on the 2,5-Dihydrothiophene 1,1-dioxide (Sulfolene)
Challenge Submission

Analog Justification

The submitter proposed to use data for the saturated analog sulfolane to fill data gaps for the sponsored substance. The test plan does not adequately describe why these two substances are expected to be toxicologically similar and why data for sulfolane would be adequate to satisfy the health effects endpoints for sulfolene.

The available mammalian toxicologic data on sulfolene and sulfolane offer weak support for the analog proposal. Comparability of acute and negative genetic toxicity alone is generally not sufficient. While matching repeated-dose studies can offer sturdy support, in this case the lack of target organ data in the sulfolene study (only body weight and mortality were examined) renders it less useful in this respect.

The existing description of the reactivities of sulfolene and sulfolane is incomplete, unclear and confusing. The test plan states that “these close structural analogs differ ONLY [emphasis added] in the presence of a carbon-carbon double bond versus a single bond in the thiophene ring structures.” This is misleading, for particularly in a very small molecule such a difference is substantial. From the statement “[t]he double

bond of sulfolene is also located across from the sulphone functional group, which makes these carbon atoms at the double bond an excellent site for nucleophilic attack", it is unclear in the absence of similar examples of transannular effects or other information how the sulfone will significantly affect the double bond in sulfolene and why it will make what is anticipated to be a relatively electron-rich double bond "an excellent site for nucleophilic attack." The cited sulfolane metabolism information is sketchy: for example, the test plan refers to the observed hydroxylation at carbon number three without stating whether the hydroxylation was exclusive to the 3-position, describing any ensuing transformations, or addressing materials balance, and no robust summary was provided. There is no explanation of why attack at a double bond and at a single bond would, unexpectedly, give the same products, as the discussion seems to imply. The reference to "hydrolysis of the double bond" is confusing.

For ecotoxicity, the SIDS-level endpoints were adequately addressed by data on the sponsored chemical.

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient, and water solubility)

The data for melting point, partition coefficient, and water solubility are adequate for the purposes of the HPV Challenge Program.

Boiling point. The estimated boiling point provided is not adequate for the purposes of the HPV Challenge Program. Estimated values are only acceptable if above 300 °C. The large difference between the measured value of 285 °C and the estimated value of 198.5° C for sulfolane also suggests that an estimated value for sulfolene will be significantly in error. The submitter needs to provide a measured boiling point value for sulfolene. If sulfolene decomposes below 300 °C, then the submitter needs to provide a measured decomposition value or range.

Vapor pressure. An estimated vapor pressure is not adequate for the purposes of the HPV Challenge Program; the use of estimated values introduces uncertainties that then become magnified in modeling applications. The submitter needs to provide a measured vapor pressure for sulfolene.

Environmental Fate (photodegradation, stability in water, biodegradation, and fugacity)

The data for these endpoints are adequate for the purposes of the HPV Challenge Program.

Stability in water. Although EPA agrees that sulfolene lacks hydrolyzable functions, the submitter needs to incorporate this information in the sulfolene robust summary.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

The submitted data for the acute and genetic toxicity endpoints are adequate for the purposes of the HPV Challenge Program. The submitter's use of sulfolane data to address data gaps for sulfolene is not well supported (see Analog Justification comments). The submitter needs to supply adequate additional information or provide test data for sulfolene (combined repeated-dose/reproductive/developmental screening test according to OECD TG 422), as well as address deficiencies in the current robust summaries.

Repeated-Dose Toxicity. For sulfolene, data for body weight and mortality were submitted for this endpoint. These data are inadequate for the purposes of the HPV Challenge Program. The submitter needs to provide data on clinical biochemistry, histopathology and necropsy with organ weights, some of which may be available from the study on carcinogenicity.

Ecological Effects (fish, invertebrates, and algae)

The data are adequate for the purposes of the HPV Challenge Program. The submitter needs to address deficiencies in the robust summaries.

Specific Comments on the Robust Summaries

Health Effects

General. The purity of the test substance needs to be stated for several studies.

Acute Toxicity. For the acute inhalation study, the saturation concentration needs to be stated. Data or a justification are needed to confirm that the concentration of isopropyl alcohol present in the test substance mixture does not contribute to any observed toxicity.

Genetic toxicity (gene mutations). The criteria for a positive response need to be stated and any statistical methods used need to be documented in the robust summaries.

Ecological Effects

Fish, invertebrates, algae. Missing study details in the summaries for sulfolene include test substance purity and total organic carbon (fish and invertebrates).

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.